REMARKS

Claims 77-86, 88-95, 97-101, 103-123, 125-131 and 133-155 were pending in the present application. Upon entry of the present amendment, claims 77, 85, and 95 are amended and claims 78-79 are cancelled without prejudice, and claims 156-177 are new claims. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. The Applicants expressly reserve the right to file continuation and divisional applications claiming priority to the present application. Support for the new and amended claims can be found throughout the specification and claims as originally filed and in particular on page 5, in its entirety; page 21, lines 5-13; page 23, lines 1-5, page 25, lines 8-17, page 26, lines 2-9, page 28, lines 17-20, Examples 1, 3, and 15, and Figure 20. No new matter is believed to have been added.

The Applicant notes that the Examiner has found claims 81-83, 111, 112 and 119-121 to be free of the art for all recited species. The Applicant further notes that the Examiner has found claims 88 and 125 to be free of the art with regard to the elected species.

Regarding the Supplemental Information Disclosure Statement

A supplemental Information Disclosure Statement is co-filed herewith. The Applicants respectfully request that the Examiner review the cited references, make them of record in the present application and return the initialed form PTO-1449.

Priority

The Applicants note that in the second recitation of the abandoned priority application serial number, the Examiner recited the incorrect U.S.S.N. 08/939,874. The corrected serial number is 08/751,888.

Claim Objections

Claims 81-83, 111 and 112 have been objected to for depending on a rejected claim, but would be allowable if rewritten in independent form including all of the limitations of the rejected base claim.

The Applicant acknowledges the Examiner's indication of allowable subject matter.

Rejections under obviousness-type double patenting

A. Claims 113-117, 126, 128-130, 134 and 135 are rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 6 and 7 of U.S. Patent No. 5,795,587 ('587) in view of Wu et al. and Mack et al.

The Applicants respectfully traverse this rejection.

The Applicants assert that the above-listed claims are non-obvious in view of the references cited by the Examiner. The Applicants note that claims 6 and 7 of the '587 patent recite a complex and method for producing nucleic acid/lipid/*polycation* complexes, where the polycation is poly-l-lysine. These claims do not include a polycationic polypeptide *salt*. Neither Mack nor Wu teach the use of a polycationic polypeptide *salt*, either. Further, as is clearly described throughout the present application, inclusion of a polycationic polypeptide *salt* in the claimed complexes and methods unexpectedly and greatly increases transfection efficiency over both nucleic acid/lipid and nucleic acid/lipid/*poly-l-lysine* (*i.e.*, nucleic acid/lipid/*polycation*) complexes (see page 23, lines 10-18; page 43, lines 7-15 and 26-28). Neither claims 6 and 7 nor Wu et al. or Mack et al. teach or suggest the unexpected and enhanced transfection efficiency of the claimed complexes and methods due to the inclusion of polycationic polypeptide *salts*.

B. Claims 122, 123 and 127 are rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claim 6 of U.S. Patent No. 5,795,587, Wu et al. and Mack et al. as applied to claims 113-117, 126, 128-130, 134 and

135 above, and further in view of Birnstiel et al. The Applicants respectfully traverse this rejection.

As stated above regarding the rejection of claims 113-117, 126, 128-130, 134 and 135, the Applicants assert that claims 122, 123 and 127 are not obvious in view of claim 6 of U.S. Patent No. 5,795,587, Wu et al. and Mack et al. Applicants also do not believe that the addition of Birnsteil renders the claims obvious. There is nothing in Birnsteil that teaches or suggests that substitution of a polycationic polypeptide *salt* would offer superior results to the complexes of claim 6 and no suggestion to combine the polycationic salts of Birnsteil with the complexes of claim 6.

The Examiner cites Birnstiel, col. 18, line 66 to col. 19, line 25, for the proposition that protamine sulfate (a polypeptide salt) and polylysine (a polypeptide) may be used interchangeably in complexes comprising a targeting ligand and a polycationic polypeptide for condensing DNA. *However, Birnstiel in summarizing the results states that the efficiency of the protamine sulfate polypeptide salt conjugate was only about one-tenth of the efficiency of the polylysine polypeptide conjugates.* See column 4, lines 11 to 19. Therefore, one of ordinary skill in the art would not be motivated to substitute the polypeptide (poly-L-lysine) in the conjugates of Mack and Wu and claim 6 of the '587 patent with the polypeptide *salt* (protamine sulfate) of Birnstiel.

Accordingly, in light of the remarks above, the Applicants respectfully requests withdrawal of the above-listed rejections (A-B).

Rejections under 35 U.S.C. § 112, first paragraph

Claims 113-123, 125-131 and 133-153 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for methods of delivering *in vitro* or systemically *in vivo* a composition comprising at least one lipid species, a polycationic polypeptide salt, and a reporter gene, and for methods of delivering directly to the site of a tumor

a composition comprising at least one lipid species, a polycationic polypeptide salt, and an E1A gene, as taught in US Pat. No. 6,008,202, wherein the composition has a net positive charge, allegedly does not reasonably provide enablement for methods of delivering therapeutic genes systemically, or for methods of delivering the E1A gene in compositions comprising a net neutral or negative charge. The specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Applicants traverse this rejection of claims. To object to a specification on the grounds that the disclosure is not enabling, the Examiner must provide evidence or technical reasoning substantiating those doubts. The Examiner has not provided evidence or technical reasoning as to why the claimed invention is not enabled. Therefore, Applicants respectfully submit no *prima facie* case of non-enablement has been made.

Assuming *arguendo* that a *prima facie* case of non-enablement has been made, which Applicants don't concede, Applicants provide the following arguments. In order to satisfy the requirements of Section 112, first paragraph, a patent application must teach one of ordinary skill in the art how to make and use the claimed invention. It is well established that enablement is not precluded by the need for some experimentation. As stated in M.P.E.P. Section 2164.01, an analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention, and whether the experimentation needed to practice the invention is undue or unreasonable. Applicants submit that it would not require undue or unreasonable experimentation for one of skill in the art to practice the claimed invention.

As conceded by the Examiner, the specification is enabling for methods of delivering *in vitro* or systemically *in vivo* a composition comprising at least one lipid species, a polycationic polypeptide salt, and a *reporter* gene, and for methods of delivering directly to the site of a tumor

a composition comprising at least one lipid species, a polycationic polypeptide salt, and an E1A gene, as taught in US Pat. No. 6,008,202. Detailed protocols and working examples are provided for the preparation of the complexes (see Examples 1-18) and their delivery *in vivo* and *in vitro*. Additionally, the specification clearly teaches that the claimed complexes have properties which make them suitable for *in vivo* delivery and also teach the skill artisan how to assay to confirm that the complexes produced have these properties.

Complexes which fall within the scope of the claims, as taught in the specification, incorporate condensed nucleic acid. Condensation of the nucleic acid not only contributes to the resulting small size of the claimed complexes, but also protects the nucleic acid from degradation by serum proteases, therefore increasing their serum stability and circulatory half-life. The size of the complexes also keeps the complexes from being taken up and cleared by the RES (reticuloendothelial) system, again leading to a longer circulatory half-life. However, despite the size and physical characteristics of the claimed complexes which are described and demonstrated in the specification, the Examiner asserts that the Applicants have not enabled the *delivery* of a *therapeutic* gene.

Applicants disagree with the Examiner's allegation. First of all, Section 112, first paragraph does not require a working examples of the delivery of every species of nucleic acid falling within the claims, or evidence of clinical efficacy and does not require that the specification provide guidance as to specific administration routes, such as oral administration, intravenous injection or intramuscular injection, in order for a claim to be enabled. Section 112, first paragraph requires that a patent application teach one of ordinary skill in the art how to make and use the claimed invention. The Applicants note that on page 9 the Examiner states "it is clear that one can use the claimed invention to deliver reporter constructs and to achieve detectable expression of reporter genes" and it is well known in the art that reporter nucleic acids are efficient and effective models for predicting the success of the delivery and expression of nucleic acids with other functions. Therefore the working examples provided in the specification

which, the Examiner concedes, are enabling for the *in vitro* and *in vivo* delivery of the reporter genes using the claimed complexes should be enabling for the delivery of other nucleic acids.

Specifically, the specification provides guidance as to the preparation and purification of the complexes beginning at page 20, lines 13-21; page 23, line 19 through page 26, line 23; in the Experimental Methods beginning on page 28, lines 11 through page 29, line 15; page 31 (Example 2) and page 39, line 21 through page 40, line 20. The specification provides guidance regarding the physical characterization and stability of the complexes in the specification at page 25, line 8 through page 26, line 13; and in Examples 1 and 3. The specification also discloses the assays and working examples for determining the transfection efficiency and biological activity of the complexes. See, for example, Figures 3-19 and 21-24; page 25, lies 17-25; page 26, lines 14-23; page 29 line 16 through page 30, line 4; page 40 line 21 through page 41, line 28; and Examples 4-10, 12-14, and 16-18. The specification provides guidance as to administration of the complexes *in vivo*. See, *e.g.*, Examples 7, 12, and 17-18. Therefore, the specification provides guidance as to making and using the claimed invention. The Examiner has not pointed to any evidence that the claimed complexes, with their associated physical characteristics, would not be able to deliver nucleic acid to cells as described and claimed.

The Examiner asserts on pages 9-10 of the Office Action that the invention as claimed reads upon gene therapy. Further, that in order to enable the full scope of the claims the nucleic acid delivered by the complex must be used as a drug. The Applicants reiterate that the pending claims are not directed to methods of treatment, but to compositions and methods for the delivery of nucleic acids to cells or to an individual.

As basis for the Section 112, first paragraph rejection, the Examiner alleges that gene therapy was unpredictable at the time of the invention and that targeting to desired tissues *in vivo* continues to be unpredictable. As support for this Section 112, first paragraph rejection of claims, the Examiner relies on Orkin (Report and Recommendations of the Panel to Assess the NIH Investment of Research on Gene Therapy, 1995), Verma et al. (*Nature* (1997) 389:239-

242), Anderson (*Nature* (1998) 392: 25-30), Deonarain (1998, Expert. Opin. Ther. Pat. vol. 8 pages 53-69) and Crystal (1995, Science, 270:404-410), as indicating that the problems hampering gene therapy include the ability to target a gene to a population of cells, express it at adequate levels for long enough periods of time, and regulate it.

The references cited by the Examiner fail to provide specific evidence that one of ordinary skill in the art would not have been able to make and use the claimed invention without undue experimentation. The specification provides guidance as to preparing nucleic acid/lipid/polycationic polypeptide salt complexes and using said complexes *in vitro* and *in vivo*.

On page 12 of the Office Action the Examiner states that "in the absence of a targeting ligand, one of skill in the art would reasonably expect that the affinity of the net neutral or negative compositions for a given cell would be less than that of a positively charged composition." Firstly, the Applicants would like to point out that rejected claim 136 incorporates the additional element of a targeting factor, claims 137-146 are dependent claims which incorporate the targeting factor of the complex of claim 77, which also incorporates a targeting factor, and dependent claims 147-153 also incorporate targeting factors. Claims 131, 133, 137, 138, and 142-143 incorporate shielding moieties such as PEG (see page 21, lines 11-13), which enhance the circulatory half-life of the complexes and would reduce charge interactions associated with the complex. Additionally claims 126 and 127 incorporate cationic lipids, which, as one of the skill in the art would be aware, would lead to a positively charged surface for the complex.

The Examiner does not provide any *specific* reasoning as to why the claimed complexes, especially those as pointed out above, will not behave as shown by the working examples provided in the specification, but instead generically states that "the affinity of the net neutral or negative compositions for a given cell would be *less* than that of a positively charged composition." There is no reasoning that would show that the claimed complexes would *lack* affinity for cells. Each of the above-listed elements, targeting factors, shielding moieties and

cationic lipids, would serve to overcome any reduced affinity for cells described by the Examiner, while the physical characteristics of the complex itself promote a longer circulatory half life as described above.

Additionally, the Applicants have shown throughout the specification that the inclusion of the polycationic polypeptide *salt* in the complex greatly increases transfection affinity over both nucleic acid/lipid and nucleic acid/lipid/poly-l-lysine complexes (see page 23, lines 10-18; page 43, lines 7-15 and 26-28). Despite the greater efficiency of these complexes as described throughout the specification the Examiner has not provided any clear reasoning of specifically why the complexes as claimed will not work as described in the specification, citing only the *"unpredictability"* of the field of the invention.

Regarding therapeutic effect, the Examiner concedes on page 13 that the Applicants have shown that the complexes containing E1A can "treat" one disease. The specification provides guidance as to how make and use the claimed invention and the Examiner fails to provide a *prima facie* case as to support the statement doubt that another therapeutic gene would not be behave similarly to the exemplified E1A gene.

Additionally, the Applicants would like to point out that the tumors formed in Examples 17 and 18 are not solid tumors which are treated by intratumoral injection, but rather ascites tumors which are not solid and can metastasize. The Applicants submit that the effectiveness of the delivery of the nucleic acid (E1A gene) is representative of treatment with other therapeutic genes and reporter genes using complexes with the physical characteristics of the claimed complexes and, further, that the Examiner has not specifically given reasons or shown why the claimed complexes would not work as described.

Therefore, in view of the arguments and evidence presented above, Applicants submit that the claimed invention is in full compliance with Section 112, first paragraph and respectfully request withdrawal of the Section 112, first paragraph rejection of claims 113-123, 125-131 and 133-153.

Rejections under 35 U.S.C. § 102

Claims 77-79, 89, 93, 94, 98-100, 104, 107-109, 139-141 and 144-146 are rejected under 102(b) as being allegedly anticipated by Mack et al. The Applicant respectfully traverses this rejection.

Independent claims 77 and 98, and therefore their dependent claims, are directed to compositions and methods requiring a nucleic acid/lipid/polycationic polypeptide *salt* complex, where the complex further comprises a targeting factor directed to a cell surface molecule. Mack et al. discloses, as summarized by the Examiner, methods pertaining to complexes comprising asialoglycoprotein-modified polylysine, plasmid DNA and cationic lipids, where the polylysine is covalently modified, attaching asialoglycoprotein.

The Applicant cannot find any teaching in Mack et al. directed to the inclusion of polycationic polypeptide *salts*. The experimental methods section of the reference discloses only the use of poly-l-lysine. As such, the reference does not teach each limitation of the independent claims 77 and 98 and therefore does not anticipate claim 77 or 98, or their respective dependent claims.

In light of the above remarks, the Applicant respectfully request withdrawal of the rejection of claims 77-79, 89, 93, 94, 98-100, 104, 107-109, 139-141 and 144-146 under 35 U.S.C. §102.

Rejections under 35 U.S.C. § 103

While the Applicants do not agree with the basic assertions put forth by the Examiner with respect to the rejections under 35 U.S.C. §103, in the interests of efficiently moving the prosecution of the present application forward, Applicants provide the comments appearing below.

A. Claims 80, 84-86, 91 and 103 are rejected under 103(a) as being allegedly unpatentable over Birnstiel et al. in view of Mack et al. The Applicant respectfully traverses the rejection.

Applicants assert that claims 80, 84-86, 91 and 103 are not obvious in light of the cited references. Further, there is no motivation to combine the cited references. Mack, as described above, teaches targeting factor-polylysine complexes with or without lipid. Birnstiel et al., characterizes protamine sulfate (polypeptide salt)-targeting factor/nucleic acid complexes as being one-tenth as efficient as equivalent polylysine conjugates (polypeptide) (col. 4, lines 15-20). One of skill in the art would not be motivated to combine the protamine sulfate (polypeptide salt)-targeting factor polycations of Birnstiel et al. with the polypeptide-containing complexes of Mack, because Birnstiel teaches that the polypeptide salt complexes are less effective in the transfection of nucleic acids. As stated in the Applicants' specification, and as highlighted on page 43 (lines 9-15) and in Examples 10 and 14, the protamine salt (polycationic polypeptide *salt*) shows unexpected transfection efficiency relative to polylysine, which is particularly unexpected in light of the teachings of the above references. There is nothing in the cited references which would suggest to one of skill in the art that there was a likelihood of success for the combination suggested by the Examiner.

B. Claims 88 and 125 are rejected under 103(a) as being allegedly unpatentable over Hung et al., in view of Trubetskoy et al., Mack, and Kern et al. The Applicant respectfully traverses the rejection.

The Applicants assert that claimed complexes and methods are not obvious in light of the cited references and that there would have been no motivation for one of skill in the art to combine the many references recited by the Examiner. Indeed, Mack and Trubetskoy disclose the use of polylysine, not polylysine *salt*. Neither Kern nor Hung overcome this deficiency. None of the above references teach or suggest that selection of polycationic polypeptide *salt* would preferentially increase delivery of nucleic acid to cells, or, that the combination of polycationic polypeptide *salt*/lipid/nucleic acid and targeting factor would result in the claimed complexes which have the physical characteristics (*e.g.*, size, etc.) and unexpectedly high transfection efficiency as described in the specification.

C. Claims 105, 113-117, 126, 130, 134-136 and 151-153 are rejected under 103(a) as being allegedly unpatentable over Wu et al. in view of Mack et al. The Applicant respectfully traverses the rejection.

The Applicants assert that claimed complexes and methods are not obvious in light of the cited references. Neither Wu nor Mack teaches the use of polycationic polypeptide *salts*. Neither Wu nor Mack suggests that a combination of polycationic polypeptide *salt*/lipid/nucleic acid and targeting factor would result in the claimed complexes which have the physical characteristics (*e.g.*, size, etc.) and associated unexpectedly high transfection efficiency as described in the specification.

D. Claims 90, 92, 101, 106, 127, 129 are rejected under 103(a) as being allegedly unpatentable over Wu and Mack as applied to claims 105, 113-117, 126, 130, 134-136 and 151-153 above and further in view of Trubetskoy et al. and Harris et al. The Applicant respectfully traverses the rejection.

The Applicants assert that claimed complexes and methods are not obvious in light of the cited references. As recited above, neither Wu nor Mack teaches the use of polycationic polypeptide *salts*. Harris does not remedy the lack of teaching or suggestion for use of a polycationic polypeptide *salt*. Although the Examiner asserts that Trubetskoy teaches the complexes containing a polycationic polypeptide salt, this is not correct. The DNA/lipid complexes contained Ab-NPLL, *i.e.*, antibody conjugated to N-terminal modified polylysine (a polypeptide, not a polypeptide salt). Therefore, the Applicants fail to see how the combination of these references could render the claimed compounds and methods obvious.

E. Claims 118, 122, 123 and 128 are rejected under 103(a) as being allegedly unpatentable over Wu and Mack as applied to claims 105, 113-117, 126, 130, 134-136 and 151-153, and further in view of Birnstiel et al. The Applicant respectfully traverses the rejection.

The Applicants assert that claimed complexes and methods are not obvious in light of the cited references. Neither Wu nor Mack teach or suggest the use of a polycationic polypeptide *salt*. Birnsteil does *not* teach or suggest that there is any advantage in using the polypeptide *salts* over polypeptide. Thus, there is no motivation to select the polycationic polypeptide *salts* of Birnsteil and replace the polypeptides of Wu or Mack.

F. Claims 95, 97, 131, 133, 137, 138, 142, 143, 147-150, 154 and 155 are rejected under 103(a) as being allegedly unpatentable over Wu and Mack as applied to claims 105, 113-117, 126, 130, 134-136, and 151-153, and further in view of Torchilin et al. The Applicant respectfully traverses the rejection.

The Applicants assert that claimed complexes and methods are not obvious in light of the cited references. Neither Wu nor Mack teach nor suggest the use of a polycationic polypeptide *salt*. This deficiency is not rectified by Torchlin which, as cited, does not mention polycationic polypeptide salts.

In light of the above arguments, Applicants assert that the claims are not obvious and request withdrawal of the above-listed rejections (A-F) under 35 U.S.C. §103.

CONCLUSION

Applicant has, by way of the amendments and remarks presented herein, made a sincere effort to overcome rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 226272002201. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: August 26, 2003 By: _____

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